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WORKING PARTY ON HERBAL MEDICINAL PRODUCTS

POINTS TO CONSIDER ON THE BIOPHARMACEUTICAL CHARACTERISATION OF HERBAL MEDICINAL PRODUCTS

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.eu.int http://www.emea.eu.int
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Draft Points to consider on the biopharmaceutical characterisation of herbal medicinal products

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1. Introduction

In contrast to chemically defined medicinal products, the biopharmaceutical quality and behaviour of herbal medicinal products (HMPs) are often not well documented. In most cases an in vitro / in vivo biopharmaceutical characterisation is complicated by the complex composition of herbal drug preparations, the extensive metabolism of their constituents and the resulting analytical difficulties. The active substance of HMPs is defined to be the whole herbal drug preparation (e.g. the extract) in its entirety.

The following considerations apply to immediate release solid dosage forms with systemic action containing preparations from the same herbal drug.

In many cases it may be assumed that a complete and rapid dissolution of the herbal drug preparation, e.g. extract, from a solid oral formulation is a prerequisite for a non-problematical bioavailability and clinical efficacy of HMPs. Some preparations such as lipid extracts and essential oils, however, are not easily soluble and do not dissolve completely from the pharmaceutical formulation. Such preparations and formulations may be more indicative of biopharmaceutical problems.

The present Points to consider document proposes some scientific aspects and strategies concerning biopharmaceutical studies for HMPs. They should be read in conjunction with other CPMP guidance related to the biopharmaceutical characterisation of medicinal products, especially the CPMP "Note for guidance on investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98), as well as in conjunction with the CPMP "Note for guidance on quality of herbal medicinal products" (CPMP/QWP/2819/00) and the CPMP "Note for guidance on specifications: test procedures and acceptance criteria for herbal drugs, herbal drug preparations and herbal medicinal products" (CPMP/QWP/2820/00).

2. Classification of active substances in HMPs as a prerequisite for biopharmaceutical characterisation

As the whole herbal drug preparation is regarded as the active substances, several types of preparations, depending on the pharmaceutical-analytical, pharmacological-toxicological and clinical findings, can be identified. In the case of extracts, the European Pharmacopoeia defines the following types of extracts:

A **Standardised** extracts containing constituents (single or groups) that are solely responsible for the acknowledged and documented therapeutic activity. Standardisation (adjustment) to a defined content is acceptable (e.g. standardised Senna leaf dry extract) using inert excipients or preparations with a higher or lower content.

B1 **Quantified** extracts containing chemically defined constituents (single or groups) possessing relevant pharmacological properties (active markers). These substances are likely to contribute to the clinical efficacy; however, evidence that they are solely responsible for the clinical efficacy is not yet available (e.g. extracts of Ginkgo, St. John's Wort). The characterisation of these extracts should take into consideration as far as possible the particular state of knowledge concerning the documented efficacy, quality and safety of an extract. Standardisation by

blending different lots of an herbal drug before extraction or by mixing different lots of herbal drug preparations is appropriate/acceptable. Adjustment /standardisation using excipients is not acceptable.

B2 **Other** extracts containing no constituents documented as being determinant or relevant for efficacy, or as having pharmacological or clinical relevance. In these cases, chemically defined constituents (markers) without known therapeutic activity, may be used for control purposes (e.g. Valerian or Stinging nettle root extract). These markers may be used to monitor good manufacturing practice or as an indicator for the assay of the drug product.

The European Pharmacopoeia classification of extracts is useful to determine the scientific level and future efforts for a biopharmaceutical characterisation of HMPs. Similar considerations should apply to other herbal drug preparations such as powders used in e.g. tablets or capsules.

3. Special aspects of HMPs in biopharmaceutical characterisation

HMPs are in many cases based on herbal drugs and preparations such as extracts used for a long period of time. Their use is often described in literature but it is not based on systematic pre-clinical and clinical studies. HMPs described in bibliographic documentations may show great differences in the extracts used, the dosage forms and strengths. This raises the question of the clinical relevance of existing differences and thus, the biopharmaceutical characterisation and bioequivalence of such products.

In order to decide on the type and on the extent of tests related to the biopharmaceutical characterisation and on the need of bioequivalence studies, the differences of extracts described in literature and the type of extracts, in the sense of "conventional extract" described in Pharmacopoeias etc. or "purified extract", should be considered. A reduced set of biopharmaceutical tests may be acceptable if a wide range of different "convential" extracts or preparations corresponding to Type B or C have been widely used and are described in the literature that supports the safety and efficacy of a product.

4. Implementation of the definitions of CPMP-Guideline 1401/98 for HMPs

4.1 Considerations related to the active substance(s)

The definitions of the EMEA CPMP Note for Guidance on BA/BE address primarily chemically defined active substances and finished products.
In contrast to synthetic active substances the composition of an herbal drug preparation is determined by the manufacturing process (product by process) and the quality of the herbal drug.
In the present state of technical development, biopharmaceutical tests are mainly based on analytical parameters. However, having in mind the complex composition of herbal drug preparations, biological testing systems are expected to add valuable information on the comparability of herbal drug preparations and HMPs.

For herbal drug preparations corresponding to class A, it is accepted that defined constituents are responsible for the therapeutic activity. Herbal drug preparations originating from the same herbal drug, but prepared with different solvents, or by different manufacturers, or by different methods of extraction may be considered to be "pharmaceutical alternatives" if the quantity of constituents with known therapeutic activity is identical and the drug to extract ratio is comparable to the reference preparation*.

For herbal drug preparations corresponding to class B1, a preparation may be classified as a "pharmaceutical alternative" if the specifications related to the "pharmacologically active markers", the extraction solvent and the drug : extract ratio are the same and if no differences in solubility exist, as compared to the reference preparation / product*.

For herbal drug preparations corresponding to class B2, a preparation may be classified as a "pharmaceutical alternative" if the extraction solvent and the drug : extract ratio are the same and if no differences in solubility exist, as compared to the reference preparation / product*.

4.2 Considerations related to the finished HMP

Different formulations (e.g. coated tablets or soft gelatine capsules) using the same active constituents may not be regarded as pharmaceutical equivalents without considering of the dissolution characteristics of the extract.

4.3 Solubility

For "immediate release" herbal medicinal products the solubility of the whole extract (Type B2), "active markers" (Type B1) or constituents with known therapeutic activity (Type A) may be regarded as crucial characteristics for a biopharmaceutical comparison with the reference product.

4.3.1 In vitro dissolution tests with HMPs

For HMPs corresponding to Type A, the in vitro release of the constituents with known therapeutic activity should be compared with the reference product*. Pharmaceutical equivalence may be accepted if in both products the in vitro release of constituents with known therapeutic activity exceeds 90%. In the case of a low in vitro-release or if the constituents have a low solubility, bioequivalence studies may be necessary.

For HMPs corresponding to Type B1, the in vitro release of "active markers" and solubility of the extract should be compared with the reference product*. Pharmaceutical equivalence may be accepted if both parameters in both products exceed 90%. In the case of a low in vitro-release or low solubility, additional clinical safety studies or bioequivalence studies may be necessary.

For HMPs corresponding to Type B2, the solubility of the extract should be compared with the reference product*. Pharmaceutical equivalence may be accepted if solubility in both products exceeds 90%.

If the solubility of the extract cannot be tested, the release of (an) appropriate marker(s) should be compared. The appropriateness of the marker for the biopharmaceutical characterisation must be justified.

If no appropriate marker can be found, a comparison of disintegration profiles may be acceptable. The applicant has to justify why a marker substance could not be identified and why additional studies on clinical safety or bioequivalence are not necessary.

* Reference: In selecting a reference for well-established HMP the level of evidence available and the extent of use of that product should be considered. If comparable data are available for several HMP, the choice of the reference must be justified by the applicant.